IMMUNOHISTOCHEMISTRY OF NEUROENDOCRINE NEOPLASMS OF THE BRONCHOPULMONARY TRACT AND SKIN
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I. NEUROENDOCRINE NEOPLASMS OF THE BRONCHOPULMONARY TRACT:

Bronchopulmonary neuroendocrine (NE) neoplasms encompass a wide spectrum of pathologically and clinically distinct entities which include typical carcinoids, well-differentiated NE carcinomas, and NE carcinomas of intermediate and small cell type (1,2). Typical carcinoids are predominantly centrally located. Microscopically they exhibit the classical architecture of solid cellular clusters and/or ribbons with little, if any, cellular pleomorphism. Metastases are very rare and appear only late in the course of the disease. Well-differentiated NE carcinomas have received various vague designations such as "atypical carcinoids", and have sometimes been misinterpreted as "early oat cell carcinomas". These tumors are most often peripheral and display considerable cytological pleomorphism; however, they still retain an organoid pattern (Fig. 1a). Mitotic figures are readily found but the mitotic activity is not as brisk as in NE carcinomas of intermediate or small cell type. Metastases are frequent. We have observed 2 to 5 years survival in about 50% of cases. NE carcinomas of intermediate and small cell type have a similarly aggressive course: they differ only in the size and arrangement of their cells. The NE carcinomas of intermediate cell type show solid clusters of pleomorphic cells with frequent central necrosis and peripheral palisading. The nuclei are vesicular and are at least twice the size of their small cell counterparts. The NE carcinomas of small cell type display an ill-defined architecture and consist of small atypical cells with hyperchromatic nuclei. Necrosis is a prominent feature, as is the characteristic crushing artifact. The mitotic count is brisk. Mixed forms may occur. Focally, features of squamous and glandular differentiation are not uncommon.

Ultrastructurally, bronchial carcinoids contain numerous neurosecretory
granules. Although the granules are usually round and between 150 to 250 nm in size, the size, shape, and the density of their cores vary considerably. Aggregates of intermediate filaments often coexisting with clusters of neurosecretory granules are frequently observed. Well-differentiated NE carcinomas are not conspicuously granulated. NE carcinomas of intermediate and small cell type often show interlacing cytoplasmic processes where their rather scanty neurosecretory granules tend to aggregate. They generally lack delimiting basal lamina, although carcinoids regularly show a distinct basal lamina.

In the majority of the NE neoplasms of the bronchopulmonary tract, reactivity for neuron specific enolase (NSE), serotonin, and various neuropeptides, can be demonstrated immunohistochemically (Fig. 1b). Sections from paraffin blocks are usually adequate for this purpose. However, proper preservation and fixation of the tissue is critical. We have found that Bouin's is the fixative of choice for these materials. By the PAP technique, the overwhelming majority of bronchial carcinoids display reactivity for NSE, serotonin, bombesin, and leu-enkephalin. Some "ectopic" materials including gastrin, melanin-stimulating hormone, VIP, etc., are also found. The majority are immunoreactive for more than one hormone. Evaluation of single sections stained for two hormones and of step sections immunostained sequentially for multiple hormones has provided strong evidence that single cells may indeed secrete and store more than one hormone (3). This observation seemingly reflects the heterogeneity of the neurosecretory granules disclosed by electron microscopy. The intensity and distribution of the immunostaining are often notably heterogeneous (4). Well-differentiated NE carcinomas also produce similar materials as those of carcinoids. ACTH is often found in these tumors while it is not frequently found in bronchial carcinoids; this is at variance with the findings of others (5) and may reflect variable taxonomic criteria. In the NE carcinomas of intermediate cell type, the most frequently demonstrated material has been ACTH, followed by bombesin, leu-enkephalin, etc. Compared to the previous three tumors, the immunoreactivity for various hormone is less frequently demonstrated in the NE cell carcinomas of small cell type. The materials most frequently demonstrated are bombesin and ACTH. Occasionally immunoreactivity for serotonin, leu-enkephalin, calcitonin, somatostatin, and VIP may also be found. Immunoreactivity for more than one hormone is also observed as is the synchronous or asynchronous variability in the expression of hormones between the primary and its metastases.